EXPLORATORY RESEARCH ON FACIOSCAPULOHUMERAL DYSTROPHY

Release Date: November 8, 2000

RFA: AR-01-002

National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Neurological Disorders and Stroke

Letter of Intent Receipt Date: February 1, 2001
Application Receipt Date: March 14, 2001

THIS RFA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS RFA.

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Neurological Disorders and Stroke (NINDS) invite exploratory and developmental research grant applications (R21) that will broaden the base of inquiry on Facioscapulohumeral muscular dystrophy (FSHD).

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS led national activity for setting priority areas. This request for applications, Exploratory Research on Facioscapulohumeral Dystrophy, is related to the priority area chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic or foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal

Investigators. Participation in the program by investigators at minority institutions is strongly encouraged.

Investigators who have questions about eligibility should contact one of the program officials listed under INQUIRIES.

MECHANISM OF SUPPORT

Research projects will be supported with the exploratory/developmental research grant (R21). The Exploratory/Developmental research mechanism (R21) is used for support of creative, novel, and/or high risk/high payoff approaches that could produce innovative advances in this field. This includes feasibility studies, protocol planning, and the incorporation of new disciplines and technologies. This mechanism provides the means to acquire the necessary pilot information, to attract talented new investigators from related disciplines, and to foster the development of interdisciplinary, inter-institutional collaborative efforts among investigators with diverse training and expertise. Applicants may request up to three years of support. Applications for research at a single institution may request up to a maximum of $125,000 direct costs per year. Applications that include a consortium/contractual arrangement may request up to a maximum of $150,000 direct costs, including the facilities and administrative costs (indirect costs) of the consortium institution. These awards are not renewable. If desired, the specific aims of the R21 project may be incorporated into a research project grant application (R01) submitted prior to the termination of the R21 award.

This RFA is a one-time solicitation. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant.

Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts. Complete and detailed instructions and information on Modular Grants can be found at http://grants.nih.gov/grants/funding/modular/modular.htm.

FUNDS AVAILABLE

It is anticipated that for FY 2001, approximately $1.0 million total costs will be available for the first year of support for this RFA. This funding level is dependent upon the receipt of a sufficient number of applications of high merit and on the availability of funds. It is anticipated that up to 5 new grants may be awarded in FY 2001 under this program. Direct costs will be awarded in

modules of $25,000. Facilities and Administrative costs will be awarded based on the negotiated rates. Applicants may request up to three years of support.

RESEARCH OBJECTIVES

Background:

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common genetic disease of skeletal muscle. It affects approximately one in 20,000 persons. FSHD is an autosomal dominant disease that initially affects muscles of the face (facio), scapula (scapulo) and upper arms (humeral). Symptoms may develop in early childhood and are usually noticeable in the teenage years with 95% of affected individuals manifesting disease by age 20 years. A progressive skeletal muscle weakness usually develops in other areas of the body as well; often the weakness is asymmetrical. Life expectancy is normal, but up to 15% of affected individuals become severely disabled and eventually must use a wheel chair. Non-muscular symptoms frequently associated with FSHD include subclinical sensorineural hearing loss and retinal telangectasias. The pathophysiology of FSHD is not known. Muscle histologic changes are nonspecific for the muscle wasting. There is evidence of early inflammatory changes in the muscle, but reported responses to high dose open labeled corticosteroid treatment have been negative. Animal studies of anabolic effects of beta adrenergic agonists on models of muscle wasting led to an open trial of albuterol (a beta adrenergic agonist) in which limited preliminary results support an improvement of muscle mass and strength in FSHD. Preliminary studies of muscle cultures suggest an increased sensitivity to oxidative stress, but require further exploration.

More than 95% of cases of FSHD are associated with the deletion of integral copies of a tandemly repeated 3.3kb unit (D4Z4 repeat) at the subtelomeric region 4q35. Inheritance is autosomal dominant, though up to one-third of the cases appear to be the result of de novo (new) mutations. The deletion appears to result in global dislocation of gene expression. If the entire region is removed, there are birth defects, but no specific defects on skeletal muscle. Individuals appear to require the existence of 11 or fewer repeat units to be at risk for FSHD. Though the nature of the DNA mutation is known, it has not been possible to identify a gene or mechanism that causes FSHD and a novel position effect has been postulated to explain the disease phenotype. In addition, some cases of FSHD are the result of rearrangements between subtelomeric chromosome 4q and a subtelomeric region of 10q that contains a tandem repeat structure highly homologous (95%) to 4q35. Disease occurs when the translocation results in a critical loss of tandem repeats to the 4q site. Finally, there is a large family with a phenotype

indistinguishable from FSHD in which no pathological changes at the 4q site or translocation of 4q-10q are found.

NIAMS and NINDS sponsored a conference on FSHD in May 2000. This was followed by a brief session in which researchers considered possible approaches for increasing knowledge about the pathogenesis and treatment of the disease. A brief summary may be seen at: http://www.nih.gov/niams/reports/fshdsummary.htm

Scope and Objectives:

The NIAMS and NINDS seek to broaden the base of knowledge concerning the pathogenesis of FSHD and possible therapies by encouraging exploratory research. Because exploratory projects may require a preliminary test of feasibility, this initiative will provide short-term support for such preliminary work. Each research plan should begin with a short paragraph describing the feasibility of the approach to increase knowledge about disease pathogenesis and disease processes that might be ameliorated.

Applications in response to this RFA should address issues related to characterizations and pathogenesis of FSHD. Examples of areas included in this RFA are listed below.

o Characterize the molecular pathogenesis of FSHD and elucidate the role of the 3.3 kilobase tandem repeats in maintaining of heterochromatin structure and the mechanism of tandem repeat deletions in this critical region of 4q.

o Determine the relationship between repeat length and its effect on penetrance. Determine also whether the loss of certain repeats is always associated with FSHD clinical expression, since there may be specificity in chromosomal transactions and the resulting pathogenesis.

o Determine the gene sequence and whether the repeats are acting as suppressors or insulating units. The region containing the site associated with at least 95% of FSHD cases is composed almost entirely of the 3.3 kilobase repeats, which are not translated. Few genes have been found near the multi-repeat locus, suggesting that FSHD may result from alterations in the chromatin structure. In particular, the data suggest that you need a minimum size of repeats in order to have a compact heterochromatin structure.

o Clarify how similarity of regions on chromosomes 4 and 10 may relate to FSHD. There is a region on chromosome 10 that appears to be largely identical (95% homology) to that on chromosome 4 at the FSHD locus (4q35). Studies on affected and unaffected populations show that there is a high amount of exchange between the homologous regions on chromosomes 4 and 10. Although disease has never been associated with alterations on chromosome 10, the frequency of such exchanges may be related to the high proportion of new (i.e., non-familial) cases of FSHD encountered.

o Characterize changes in muscle as the disease develops. This would be facilitated by non-invasive ways of looking at the muscle and microvasculature in affected and non-symptomatic regions. Studies using improved imaging techniques would provide better assessment of patient muscle, including vasculature, that is pre-atrophic.

o Determine basis of differential involvement of muscles, reflected by the regional pattern of disease. Comparison of muscle groups might show the cause of relative specificity of affected muscles. Comparing expression patterns of RNA and protein in affected and non-affected muscle will provide insights into alterations occurring as the disease progresses.

o Explore the role of inflammation in FSHD. While FSHD has been described as the most inflammatory form of muscular dystrophy, there is no evidence that disease severity is lessened by administration of the anti-inflammatory drug prednisone. It is necessary to explore the relationship between inflammatory cells, muscle cell death, and blood vessels.

o Study properties of muscle cells derived from affected tissue. Cells cultured from FSHD muscle show increased sensitivity to oxidative stress. This needs to be followed up by studies verifying that this occurs in vivo and establishing how this cellular phenotype develops.

o Determine if a nonstandard locus produces FSHD. Characterize the gene defects in the family with FSHD phenotype but no linkage to the 4q35 locus to pursue a better understanding of FSHD disease processes.

o Create new models of FSHD. The development of new models of the genetic pathogenesis of FSHD would provide a tool to research scientists in muscle biology, attracting new investigations to pursue understanding of disease pathogenesis and eventual therapies for FSHD.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm: The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the Inclusion of Children as Participants in Research Involving Human Subjects that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

LETTER OF INTENT

Prospective applicants are asked to submit, by February 1, 2001, a letter of intent that includes a descriptive title of the proposed research; the name, address, and telephone number of the Principal Investigator; the identities of other key personnel and participating institutions; and the number and title of this RFA. Although a letter of intent is not required, is not binding, does not commit the sender to submit an application, and does not enter into the review of a subsequent application, the information that it contains allows NIH staff to estimate the potential review workload and avoid conflict of interest in the review. The letter of intent is to be sent (e-mail, fax or post) to Dr. Tommy Broadwater at the address listed under INQUIRIES.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants, with the modifications noted below. These forms are available at most institutional offices of sponsored research; from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, Email: grantsinfo@nih.gov; and on the Internet at http://grants.nih.gov/grants/funding/phs398/phs398.html.

The RFA label found in the PHS 398 (rev. 4/98) application form must be affixed to the bottom of the face page of the application. The RFA label and line 2 of the application should both indicate the RFA number. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review.
The sample RFA label available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf has been modified to allow for this change. Please note this is in pdf format.

For purposes of identification and processing, item 2a on the face page of the application must be marked "YES" and the RFA number "AR-01-002" and the words "EXPLORATORY RESEARCH ON FACIOSCAPULOHUMERAL DYSTROPHY" must be entered on the face page.

BUDGET INSTRUCTIONS

Modular grant applications that include a consortium/contractual arrangement may request direct costs in $25,000 modules up to a yearly maximum of $150,000 direct costs, including the facilities and administrative costs (indirect costs) for the consortium institution. Applications proposing research at a single institution may request up to a maximum of $125,000 direct costs per year.

The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

o FACE PAGE - Items 7a and 7b should be completed, indicating Direct Costs (in $25,000 increments up to a maximum of $125,000 for research at a single institution, or up to a maximum of $150,000 for research involving a consortium/contractual arrangement) and Total costs (Modular Total Direct plus Facilities and Administrative (F&A) Costs) for the initial budget period, and Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION - Use a Modular Grant Budget Narrative page. (See http://grants.nih.gov/grants/funding/modular/modular.htm for sample pages.)
At the top of the page, enter the total direct costs requested for each year.

o Under Personnel, list all project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided.

o For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest $1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made,

the percent effort of all personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. Include the letter of intent to establish a consortium.

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at: http://grants.nih.gov/grants/funding/modular/modular.htm.

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years;
- List selected peer-reviewed publications, with full citations.

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o PAGE LIMITATION - In keeping with the pilot/feasibility nature of the requested studies the application (aims, background and significance, preliminary data and experimental design and methods) is limited to 20 pages. Tables and figures are included in the 20-page limitation.

o APPENDIX - An appendix or additional supporting materials will not be accepted with the exception of originals of photos used in the application.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

APPLICATIONS NOT CONFORMING TO THESE GUIDELINES WILL BE CONSIDERED UNRESPONSIVE TO THIS RFA AND WILL BE RETURNED WITHOUT FURTHER CONSIDERATION.

Submit a signed typewritten original of the application and three signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC-7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must be sent to:

Tommy L. Broadwater, Ph.D.
Scientific Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-25U - MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-4952
FAX: (301)-402-2406
Email: broadwat@exchange.nih.gov

In order not to delay review, it is important that applicants comply with this request.

Applications must be received by March 14, 2001. If an application is received after that date, it will be returned to the applicant without review. Only one R21 grant application may be submitted by a Principal Investigator.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by CSR and responsiveness by NIAMS and NINDS. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened

by the NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and under a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. For this initiative, the proposed project must have the potential for developing approaches or information that may lead to significant increases in understanding or treating FSHD. In the written review, comments on the following aspects of the application will be made in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in the assignment of the overall score.

(1) Significance. Does this study address issues important to understanding and treating FSHD? If the aims of the application are achieved, how will scientific knowledge about FSHD be advanced? What will be the effect of these studies on the concepts or methods that drive research on FSHD?

(2) Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the investigator acknowledge potential problem areas and consider alternative tactics?

(3) Innovation. Does this application have the potential for ground breaking advances that may lead to new approaches to research on FSHD? Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies? If the project is not innovative but is essential to move the field forward, the applicant should mention and discuss this aspect in the proposal.

(4) Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

The initial review group will also examine the provisions for the protection of human and animal subjects, the safety of the research environment, and conformance with the NIH Guidelines for the Inclusion of Women, Minorities and their subgroups, and children as Subjects in Clinical Research.

The personnel category will be reviewed for appropriate staffing based on the requested percent effort. The direct costs budget request will be reviewed for consistency with the proposed methods and specific aims. Any budgetary adjustments recommended by the reviewers will be in $25,000 modules. The duration of support will be reviewed to determine if it is appropriate to ensure successful completion of the requested scope of the project.

AWARD CRITERIA

The following will be considered in making funding decisions:

o Scientific merit of the proposed project as determined by peer review;
o Importance of the area to understanding and treating FSHD;
o Potential for ground breaking advances that may lead to new approaches to research on FSHD; and
o Availability of funds.

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic and scientific issues to one of the following persons:

Richard W. Lymn, Ph.D.
Muscle Biology Program

National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-49E
Bethesda, MD 20892-6500
Telephone: (301) 594-5128
FAX: (301) 480-4543
Email: LymnR@mail.nih.gov

Giovanna M. Spinella, M.D.
Division of Fundamental Neuroscience and Developmental Disorders
National Institute of Neurological Disorders and Stroke
6001 Executive Boulevard, Room 2132
Bethesda, MD 20892
Telephone: (301) 496-5745
FAX: (301) 402-0887
Email: gs41b@nih.gov

Direct review inquiries to:

Tommy Broadwater, Ph.D.
Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A25U
Bethesda, MD 20892-6500
Telephone: (301) 594-4952
FAX (301) 480-4543
Email: broadwat@exchange.nih.gov

Direct inquiries regarding fiscal matters to:

Melinda Nelson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-49F, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-3535
FAX: (301) 480-5450

Email: nelsonm@mail.nih.gov

Karen D. Shields
Grants Management Branch
National Institute of Neurological Disorders and Stroke
6001 Executive Boulevard, Room 3264
Bethesda, MD 20892
Telephone: (301) 496-9231
FAX: (301) 402-0219
Email: ks26n@nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846 (NIAMS) and No. 93.853 (NINDS). Awards are made under authorization of sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke free workplace and promote the non-use of all tobacco products. In addition, Public law 103-227, the pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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